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## REMARKS

Claims 1-4, 9-11, 14, 15, 25-28, 33-35 and 38 are pending. Claims 2-4, 9 and 25-28, 33-35 and 38 have been cancelled. New claims 39-44 are added herein. Accordingly, claims 1 and 14, as amended, and dependent claims 10, 11, and 15, and new claims 39-44 are under consideration.

Claims 1 and 14 and dependent claims therefrom have been amended to better define the claimed subject matter. Support for these amendments is found in the original claims and throughout the specification. Specifically, claim 1 as amended is supported by original claims 3, 10, 14 and 16. Claim 14 as amended is supported by claim 14 as originally presented. Support for new claims 39-44 is found throughout the specification and in the original claims. New claim 39 is supported by Example 2. Support for claim 40 is found at page 4, lines 11-13, page 8, line 29 to page 9, line 6, and Example 3. Claim 41 is supported by Examples 2 and 3. Claims 42 and 44 are supported by the specification at page 8, lines 24-25 and Examples 1-3. Claim 43 is supported by Example 2. No issue of new matter is introduced by these amendments.

The above amendments are clearly indicated in the attachment entitled "MARKED UP VERSION OF THE CLAIMS."

### *Priority*

The Examiner has acknowledged applicants' claim for foreign priority based on an application filed in the United Kingdom on April 20, 1999. A certified copy of GB application number 9909066.4 is on order and will be submitted to the Examiner upon receipt.

### *Drawings*

The drawings are objected to as described in form PTO-948. Accordingly, applicants submit herewith a revised set of drawings. See Exhibit A. Entry and favorable consideration of the drawings submitted herewith is requested.

***Rejections 35 USC § 112***

Claims 1, 9-11, 14, 15, 25, 34, 25, and 38 have been rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time the application was filed. Applicants presume that the inclusion of claim 25 twice in the above rejection was due to a typographical error on the part of the Examiner and assume that the rejection was intended to be directed to claims 1, 9-11, 14, 15, 25, 34, 35, and 38. The rejection appears to be based on recitation of the phrase "inhibitor of glycolipid synthesis". Claims 9 and 25, 34, 35, and 38 have been cancelled, thereby obviating the rejection of these claims. Claim 1 and the claims depending therefrom have been amended to clarify that the inhibitor of glycolipid synthesis is N-butyldeoxynojirimycin (NB-DNJ). Claims 1, 10, 11, 14 and 15, as amended, are believed to be directed to subject matter for which the specification contains ample written description. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 10, 11, 14, and 15 under 35 U.S.C. §112, first paragraph.

Claims 1-4, 9-11, 14, 15, 25, 26, 33-35 have been rejected under 35 U.S.C. §112, first paragraph, on the basis as understood, that the claimed invention purportedly lacks sufficient enablement. Claims 2-4, 9, 25, 26, 33-35 have been cancelled, thereby obviating the rejection of these claims. Claims 1, 10, 11, 14, and 15, as amended, render apparent the glycolipid storage-related disorders treatable using the methods of the invention, and the inhibitors of glycolipid synthesis and the agents capable of increasing the rate of glycolipid degradation used in the methods and compositions of the invention.

As stated by the Examiner at page 8 of the Office Action "the art teaches treatment of type I Gaucher disease by administration of glucocerebrosidase or bone marrow transplantation". One of skill in the art would also appreciate that patients with other glycoplid storage-related disorders typified by systemic storage defects may also be treated by the methods of the invention. Such glycoplid storage-related disorders exhibiting systemic storage defects include, for example, Gaucher disease, Sandhoff's disease, Fabry's disease and Tay-Sach's disease.

Sandhoff's disease is characterized by the accumulation of lipids in the brain and other organs of the body. A number of the symptoms are related to systemic deposition of lipids. See Exhibit B. Fabry's disease is associated with deposition of lipids in a variety of organ systems, including the eye, the circulatory system, and the kidneys. See Exhibit C. Tay Sach's disease is associated with a number of symptoms including loss of muscle tone and motor skills, which reflect systemic deposition of lipids. See Exhibit D.

Thus, in addition to the symptoms associated with inappropriate lipid deposition in the central nervous system, the above-mentioned glycolipid storage-related disorders are also known to affect organ systems other than the nervous system. In view of the above, the methods of the present invention are clearly applicable to the treatment of patients with Sandhoff's disease, Fabry's disease and Tay-Sach's disease, as well as Gaucher disease, because patients with these diseases suffer from symptoms related to systemic glycolipid deposition. The methods of the present invention may, therefore, be used to advantage to alleviate adverse symptoms associated with systemic glycolipid deposition.

Moreover, the examples of the present invention which demonstrate that NB-DNJ mediates an increase in the half-life of Ceredase™, provides compelling evidence that a combination therapy of NB-DNJ and Ceredase™, for example, is of utility for treatment of Gaucher disorder. It is definitive evidence. By extension, such evidence is applicable to other glycolipid storage-related disorders, such as Sandhoff's disease, Fabry's disease and Tay-Sach's disease.

Notably, the examples of the present invention also demonstrate that in a mouse model of Sandhoff disease, Sandhoff mice responded favorably to a combination treatment with NB-DNJ and bone marrow transplantation. Thus, it will be appreciated that a glycolipid storage-related disorder shown to be treatable by bone marrow transplantation may be treated efficaciously using the methods of the present invention as described herein.

Claims 2-4 and 26 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. Claims 2-4 and 26 have been cancelled, thereby mooting the rejection of these claims under 35 U.S.C. §112, second paragraph.

In view of the above, the Examiner is respectfully requested to reconsider and withdraw the rejection of the instant claims under 35 U.S.C. §112.

***Provisional Rejection Under the Judicially Created Doctrine of Obviousness-Type Double Patenting***

Claims 1-4, 9-11, 14, and 15 have been rejected provisionally as allegedly unpatentable over claims 1 and 8 of co-pending Application No. 10/054,802 in view of Aerts et al. Claims 2-4 and 9 have been cancelled, and the remaining claims have been amended and distinguished as per the present response, so that the rejection is believed to be obviated and overcome. Withdrawal of this rejection is accordingly requested.

Claims 25, 26, 33-35, and 38 have been rejected provisionally as allegedly unpatentable over claim 10 of co-pending Application No. 09/859,928 in view of Aerts et al. Application No. 09/859,928 issued as U.S. Patent No. 6,495,570 on December 17, 2002. The cancellation of these claims renders the rejection moot, and withdrawal thereof is requested.

***Rejection Under 35 U.S.C. § 102***

The Examiner has rejected claims 1-4, 9-11, 14, and 15 under 35 U.S.C. §102(b) as allegedly anticipated by any one of Platt et al. (1998; IDS AF), Platt and Butters (1998; IDS AO), or Aerts et al. (1998; IDS AH). The Examiner posits that "there is no significant difference in the level of guidance presented" in the instant application and that of the prior art. Applicants strenuously disagree with the Examiner's position. Applicants' respectfully submit that the present invention exemplifies a method for treating a patient with a glycolipid storage-related disorder directed to the use of a combination therapy wherein N-butyldeoxynojirimycin (NB-DNJ) and enzyme augmentation are administered to the patient. The present invention is based on the surprising result that NB-DNJ can be administered effectively with either enzymes involved in glycolipid degradation or transplanted bone marrow. None of the prior art documents cited by the Examiner suggest that this would be the case.

Indeed, Platt *et al* (1998; IDS AF) state that NB-DNJ is known to be an inhibitor of lysosomal glucocerebrosidase, an enzyme required for the cleavage of Glc-Cer to glucose and ceramide. See column 10, lines 46-50. Moreover, Platt *et al* teach, as also shown in related U.S.

Patent No. 5,399,567, that the N-butyl derivative of DNJ acts as an **inhibitor of glucocerebrosidase** in a cellular environment. See column 10, lines 50-56. Also provided by Platt *et al* is direct experimental evidence demonstrating that NB-DNJ exhibits moderate inhibition of glucocerebrosidase. See Column 10, lines 56-67 and Table 5. In view of the above, these authors clearly did not appreciate that the specific combination of NB-DNJ and enzyme augmentation would be of any utility. Indeed, the disclosure of Platt *et al* would teach a skilled artisan that such a combination would be contraindicated in a method directed to treating glycolipid storage-related disorder. Thus, this reference fails to anticipate the methods of the present invention.

Platt and Butters disclose that glycolipid storage diseases, *e.g.* Gaucher disease, may be treated by enzyme replacement therapy using, *e.g.*, glucocerebrosidase, or by substrate deprivation using e.g. NB-DNJ or NB-DGJ. Platt and Butters do not teach the specific combination of NB-DNJ and enzyme augmentation. Thus, this reference fails to anticipate the methods of the present invention which are directed to the specific combination of NB-DNJ and enzyme augmentation.

Aerts *et al* comment in passing that a combination of a glucosylceramidase inhibitor and glucocerebrosidase "**may be envisioned**" for the treatment of Gaucher disease. The authors **speculate** that the administration of glucosylceramidase inhibitors may improve the efficacy of enzyme therapy but provide no evidence to support this assertion. Of note, Aerts *et al* do not disclose the specific combination of NB-DNJ and enzyme augmentation. Nor does this reference present any evidence that NB-DNJ and enzyme augmentation could be administered effectively in combination because the specification specifically teaches away from such combination use. Moreover, Aerts *et al* indicate the disadvantage of using NB-DNJ in such a combination as it is known to inhibit lysosomal glucocerebrosidase, *i.e.*, the very enzyme for which augmentation is required (see page 9, lines 1-12). Thus, this reference fails to anticipate the methods of the present invention which are directed to the specific combination of NB-DNJ and enzyme augmentation.

***Rejection Under 35 U.S.C. § 103***

The Examiner has rejected claims 25, 26, 33-5, and 38 under 35 U.S.C. §103(a) as allegedly obvious over any one of Platt et al. (1998; IDS AF), Platt and Butters (1998; IDS AO), or Aerts et al. (1998; IDS AH).

The problem solved by the present invention is the provision of therapies for the treatment of glycolipid storage disorders. None of the Platt *et al*, Platt and Butters, or Aerts *et al* either alone or in combination would lead the skilled person to combine NB-DNJ and enzyme augmentation in an attempt to solve this problem with a reasonable expectation of success.

At the priority date of the present invention there was a significant technical prejudice against combining NB-DNJ and enzyme augmentation for the treatment of glycolipid storage disorders, as NB-DNJ was a known inhibitor of glucocerebrosidase ($IC_{50}$ = 0.52mM), see, for example, the present application page 2, lines 23-29 and Aerts *et al* page 9, lines 1-12.

Surprisingly, it has been found that the co-administration of NB-DNJ and enzyme replacement does not compromise the activity of glucocerebrosidase and indeed provides an augmentation of enzyme activity. See Example 2.

In addition, the combination of NB-DNJ and enzyme augmentation in the form of bone marrow transplantation shows an unexpected synergistic effect. See Example 3.

Thus, none of the references relied upon by the Examiner (i.e., Platt *et al*, Platt and Butters, or Aerts *et al*) considered either alone or in combination would lead a skilled practitioner to the method of the present invention which is drawn to a combination of NB-DNJ and enzyme augmentation for the treatment of glycoplipid storage-related disorders.

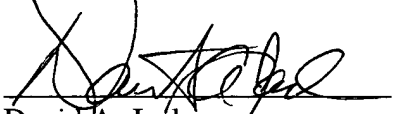
***Fees***

A check in the amount of $410.00 is enclosed for a two-month extension of time. No other fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

***Conclusion***

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Attachments: VERSION WITH MARKINGS TO SHOW CHANGES MADE
EXHIBITS A-D

## MARKED UP VERSION OF CLAIMS

1. (once amended) A method for treating a glycolipid storage-related disorder selected from the group consisting of Gaucher disease, Sandhoff's disease, Fabry's disease and Tay-Sach's disease, comprising administering a therapeutically effective amount of [an inhibitor of glycolipid synthesis] N-butyldeoxynojirimycin (NB-DNJ) in combination with an agent capable of increasing the rate of glycolipid degradation selected from the group consisting of an enzyme involved in glycolipid degradation and bone marrow transplantation.

14. (once amended) The method of claim 1, wherein the glycolipid storage-related disorder is [selected from the group consisting of] Gaucher disease[, Sandhoff's disease, Fabry's disease, Tay-Sach's disease, Niemann-Pick disease, GM1 gangliosidosis, Alzheimer's disease, stroke, epilepsy].